The relationship between amyloid deposition, neurodegeneration, and cognitive decline in dementia

Rik Vandenberghe[1,2,3]

[1]Laboratory for Cognitive Neurology, Department of Neurosciences, University of Leuven, [2]Neurology Department, University Hospitals Leuven, [3]Alzheimer Research Centre KU Leuven, Leuven Institute of Neuroscience and Disease, University of Leuven, Belgium.

Correspondence to: Rik Vandenberghe, M.D., Ph.D., Neurology Department, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium, e-mail: rik.vandenberghe@uz.kuleuven.ac.be, phone ++ 32 (0)16 344280, fax: ++ 32 (0)16 344285

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Abstract

Amyloid imaging has been approved for clinical use for measuring β amyloid plaque load in patients being evaluated for Alzheimer's disease or other causes of cognitive decline. Here we explore a multidimensional approach to cognitive decline, where we situate amyloid plaque burden among a number of other relevant dimensions, such as aging, volume loss, other proteinopathies such as TDP43 and Lewy bodies, and functional reorganisation of cognitive brain systems. The multidimensional model incorporates a 'pure AD' trajectory, corresponding to e.g. monogenic Alzheimer's disease, but leaves room for other combinations of biomarker abnormalities (e.g. volume loss without amyloid positivity) and other trajectories. More tools will become available in the future that allow one to carve out a causal-mechanistic space for explaing cognitive decline in a personalized manner, enhancing progress towards more efficacious interventions.

1 Introduction

Thanks to amyloid positron emission tomography (PET) it has become possible to measure in vivo the neuritic plaque burden in an individual's brain [1, 2, 3, 4]. Very recently, large-scale prospective longitudinal multimodal imaging datasets that incorporate amyloid imaging in hundreds of subjects have started to illuminate fundamental questions about the pathophysiology of cognitive decline in older adults, in a way that could not be imagined even 15 years ago. Longitudinal measurements of amyloid load have also been applied to assess amyloid-lowering study drug interventions, which unfortunately did not yield clinical benefit [5, 6, 7]. Paradoxically, one of the most remarkable discoveries based on amyloid imaging is the substantial portion of patients who have a clinical phenotype of amnestic mild cognitive impairment (MCI) or even clinically probable Alzheimer's disease (AD), but actually do not have an increased amyloid load [8, 9, 7, 10]. Until a few years ago clinicians may have been relatively confident about the positive predictive value of their clinical diagnoses of amnestic MCI or clinically probable AD for the presence of neuritic amyloid plaque, nevertheless 10-40% of such cases actually do not have increased amyloid burden [8, 9, 11, 10, 12].

The clinical use of amyloid imaging has been approved by regulatory authorities for the purpose of measuring β amyloid plaque load in patients under evaluation for AD. The distinction between a disease-oriented (distinction AD from non-AD) and a process-oriented diagnostic tool (assessment of amyloid load) is important: It reflects a shift towards measurements of pathophysiological processes in an individual, away from assigning cases to conventional disease categories. Without doubt a categorical diagnostic approach is appropriate for a number of diseases encountered in a

memory clinic, such as autosomal dominant AD, Huntington's disease, or syphilitic dementia, to name just a few. In the current review however we will explore the merits of a multidimensional approach [4]. The term 'multidimensional' refers to the traditional mathematical approach of multidimensional scaling, where a datapoint (a case) is plotted against a number of axes (dimensions). Such a data-driven approach respects the heterogeneity between patients as well as the overlap between seemingly distinct conventional clinical categories. According to this multidimensional view, amyloid imaging is heralding a new era where we will be able to measure multiple relevant pathophysiological dimensions in an individual on a personalized basis and tailor interventions accordingly.

A telling example for illustratory purposes is Lewy body dementia. In Lewy body dementia, amyloid PET is often positive [13, 14]. Wihtin a multidimensional mindset, a logical approach would be to apply multimodal imaging rather than to insist on assigning the case to a single diagnostic category, either Lewy body dementia or AD [15]. Multimodal imaging of volume loss, ^{18}F-fluorodeoxyglucose (FDG) PET metabolism, dopaminergic integrity and amyloid PET in a given individual enables a personalized approach to diagnosis and, hopefully, future interventions [15]. Every day clinicians encounter many similar situations, e.g. instances where cerebrovascular disease, cerebral amyloid angiopathy and AD overlap, or in the vast majority of elderly patients with cognitive decline above the age of 80.

One of the principal arguments in favor of the multidimensional model comes from genetic association studies in AD (for review see [16]) which implicate more than 30 polymorphisms pointing to a dysregulation of a multiple molecular networks beside the APP processing pathway. These are related to inflammatory, lipid processing, and cell cycle pathways, among others [16]. The most vulnerable nodes within these molecular networks are the hubs [16], one of which is the Amyloid Precursor Protein (APP). The molecular hub-and-network approach may create favorable conditions for developing more efficacious therapy, besides the amyloid-lowering strategy [7].

Population-based epidemiological studies point into the same direction. Although a strong relationship exists between dementia and the presence of neurofibrillary tangles and neuritic plaques until 75 years of age [17], this relationship becomes weaker above the age of 80, especially for neuritic plaques. In contrast, neuropathological measures of volume loss retain their strong relationship with the presence or absence of dementia over the entire age range [17]. The causes of volume loss are much broader than amyloid burden alone as will be discussed later in this review.

The purpose of the current review is to critically analyze the tripartite amyloid load, neurodegeneration and cognitive decline within a multidimensional framework. This multidimensional space

encompasses the trajectory of what has been called 'pure' AD, as specified by the sequential model triggered by amyloid proposed by Jack et al. (2013) [18]. It however also allows for combinations of biomarker abnormalities that fall outside the boundaries of the sequential model (e.g. hippocampal volume loss or episodic memory decline without amyloid positivity). As we will review, such combinations are frequent and we expect their frequency to increase as more tools become available to measure causal dimensions beyond amyloid alone.

2 Sequential model with amyloid as a trigger

The tripartite between amyloid aggregation, neurodegeneration and cognitive decline is the centerpiece of one of the most influential heuristic models of AD pathogenesis to date, the Jack et al. (2013) [18] model. This model is a translation of the amyloid cascade hypothesis [19, 20] into a sequence of changes that can be measured by contemporary techniques in vivo in humans. Its basic tenets are

1. A number of measures are grouped under a common denominator called 'neurodegeneration'. These measures include volume loss as measured with structural magnetic resonance imaging (MRI), FDG PET hypometabolism, and cerebrospinal fluid (CSF) total tau increase.

2. The panoply of in vivo measures evolve over time according to an orderly chronological sequence. The initial event is β amyloid related (as measured by means of amyloid PET and CSF Aβ42). This serves as a trigger for 'neurodegeneration' (e.g. hippocampal volume loss). Positive markers of neurodegeneration are followed by and go along with clinical symptoms, as has been demonstrated e.g. for volume loss by numerous studies [21, 22, 23, 17, 24, 25].

3. Changes over time of each of these measures are best described by sigmoidal curves. The steepness of the slope for each measure can be considered as an indication of the phase of the disease [26]. This time dimension can be expressed as years or on an 'Alzheimer's Disease Progression Scale' [27]. For clinical drug trials, ideally, one would like to include subjects when they are at a stage where the primary outcome measure is near the point of maximal rate of change.

This sequential model has been successfully applied to population-based longitudinal multimodal imaging datasets, such as the Mayo Clinic Study of Aging (MCSA) (n > 400, including cognitively intact subjects as well as > 100 MCI cases) and the Baltimore Longitudinal Study of Aging (BLSA, n > 800), and also to the Alzheimer Disease Neuroimaging Initiative (ADNI) and the Australian

Imaging, Biomarker and Lifestyle Flagship Study of Ageing (AIBL). The latter two studies have recruited cognitively intact participants from the community combined with memory clinic recruited patients with early or late MCI and early-to-moderate stage AD.

Modelling the sigmoidal changes for each of the measures on the basis of these large datasets has yielded exciting novel insights. For instance, in BLSA the episodic memory measure which changed first in healthy older adults was the total learning score of the 15-word list recall test [27]. After a period of time the delayed recall also started to decline. As subjects advanced to the clinical stage, the rate of change in delayed recall became more prominent than the rate of change of the total learning score [27]. Sigmoidal curves have also been applied to quantitative measures of neocortical thinning, an established method for analyzing structural changes in neocortex. Cortical thinning of AD vulnerable neocortical regions follows a sigmoidal curve, with the maximum speed at the inflection point around a MiniMental State Examination (MMSE) score of 21 out of 30 [24]. This is consistent across all AD vulnerable regions [28]. In contrast, hippocampal volume continues to decline (positive acceleration) until an MMSE of at least 15 out of 30 (lower limit in study) [24].

Among healthy controls and MCI patients, a higher baseline amyloid burden is associated with a higher rate of amyloid accumulation over the following years [29, 30, 31, 32], regardless of the baseline hippocampal volume [32]. Over time, amyloid positivity is associated with a higher rate of subsequent volume loss, mainly in temporal neocortex and posterior cingulate [33], in particular in cases who already have hippocampal volume loss to start with [32]. When patients have evolved into the probable AD stage, amyloid retention values are at a plateau with almost no subsequent change [31]. In the AIBL study, the timespan from a clearly negative amyloid PET to a manifestly positive, AD-like PET was estimated to be no less than 30 years [31].

The most powerful tests of the sequential model have come from longitudinal studies in subjects with autosomal dominant AD [34, 35, 36]. According to a large-scale international study of carriers of AD genetic mutations [34], amyloid deposition in precuneus occurs 28 years before symptom onset, hippocampal volume loss at about -15 years and glucose hypometabolism in precuneus at around -18 yrs. In another monogenic AD cohort, the Presenilin 1 (PS1) E280A mutation kindred (also called the Antioquia (Columbia) kindred), MCI starts on average at the age of 44 and AD at the age of 49 years [35, 36]. Fibrillar Aβ (as measured with ^{18}F-florbetapir PET) begins to accumulate in mutation carriers at a mean age of 28 years, rises steeply over the next 9 years and plateaus at a mean age of 38 years, about 6 and 11 years before the expected MCI and dementia onset. Surprisingly, in presymptomatic monogenic AD Aβ42 initially increases before it drops to a level below that seen in normal controls at around -20 yrs [34, 36, 37]. The initial Aβ42 rise is

surprising as prior to these studies the only pathological values described for Aβ42 were *decreases* compared to controls.

The sequential model captures the sequence and nature of changes that are strictly Alzheimer related, and optimally fits the disease course in monogenetic cases. However, a number of common pathophysiological processes are left out and underspecified in the sequential model of AD-related changes. These are the 'confounding problem of non-AD pathophysiologies in elderly cohorts' [18]. Likewise, the neuropathological basis of the measures subsumed under the term 'neurodegeneration' is complex. Several pathological processes converge on the same brain structures that mediate cognitive decline [22, 25]. While cross-sectional [38] and longitudinal [23] measures of MRI volume loss correlate with neurofibrillary tangles and neuritic plaque load, MRI volume reflects more than neuronal loss caused by AD pathology alone. It is also affected by aging, vascular changes or hippocampal sclerosis and many other factors [39, 40, 22, 25]. This is relevant for trial design: while selective neuronal loss would be an exquisite drug target, multicomposite measures such as MRI, FDG PET or CSF tau may have limited utility as these measures are the integral outcome of a wide variety of processes.

3 A cellular definition of neurodegeneration

Neurodegeneration refers to regionally selective neuronal loss, preceded by early neuronal dysfunction and synaptic loss. Its key feature is the selectivity for specific types of neurons in specific regions of the brain [41, 42, 43, 44]. Neuronal loss (neurodegeneration in its strict definition) is directly related to cognitive decline [45, 46, 41, 47, 48]. For that reason, neuronal loss is a process that one would definitely want to intervene against. If we could preserve neurons, clinical outcome measures would most likely be favorably affected.

Neurodegeneration is associated with the aggregation of proteins in extra- or intracellular space [49]. In AD, this consists not only of neuritic amyloid plaques and neurofibrillary tangles. Tar DNA Binding Protein (TDP)-43 proteinopathy, for instance, occurs in 50% of AD causes and is more extensive in AD than previously thought [40]. It is associated with cognitive impairment in multiple domains and can result in a phenotype that closely resembles that seen in AD [40]. Prospective community-based neuropathological studies have also highlighted the contribution of cerebrovascular lesions [50] or Lewy bodies [51] to cognitive decline in AD. According to the Vienna Transdube Aging study, the different proteinopathies make partly independent contributions to cognitive decline [52, 49]. Different combinations of proteinopathies may have a cumulative effect

until a threshold for cognitive dysfunction is exceeded and mechanisms of compensation fail [52].

One of the fundamental questions in the pathogenesis of neurodegenerative diseases is the relationship between selective neuronal loss and the intra- and extracellular proteinopathy. In AD, how does amyloid aggregation relate to selective neuronal loss? Does it cause neuronal loss or is it, like neuronal loss, a consequence of a third-party cause? Proteinopathies may also be markers of diseases that involve complex cascades of events that over time result in cognitive decline and/or dementia [16, 53].

Recent longitudinal neuropathological studies in large population-based cohorts have yielded critical insights into the relationship between brain volume loss, proteinopathies and cognitive decline that often go against commonly held views [17, 53, 40]. In a large-scale prospective population-based clinicopathological study, the Rush Memory and Aging study combined with the Religious Order studies [40, 53], AD pathologic indices explained 30 to 34% of the between-subjects variance, infarcts 1 to 3%, neocortical Lewy bodies 4 to 8%, and locus coeruleus noradrenergic neuronal density 3-6% of variance. In other words, approximately 60% of the variance in late-life cognitive decline remained unexplained by the classical neuropathological markers. The authors refer to this unexplained variance as the 'pathology-cognition gap' [53]. There have been endeavours by neuropathologists to try to measure compensatory mechanisms postmortem [53, 54]. In vivo measures however, as provided by functional MRI, may be even more appropriate as a method to bridge the pathology-cognition gap.

4 In vivo measures beyond what can be measured post mortem: Brain circuits at work (and 'at rest')

Structural or biochemical measures post mortem fall inherently short of capturing the rich dimensions of the functioning brain during life at a systems level. Functional MRI has revealed a number of important and novel insights in how cognitive brain systems at work react to amyloid-related injury and how functional connectivity drives regional vulnerability for amyloid aggregation.

4.1 Evidence of functional compensation from task-related fMRI

Among the most popular episodic memory tasks for fMRI is face-name associative learning. Subjects have to encode and subsequently retrieve a list of pairs of a face and a name. This task activates the hippocampal formation in normal controls. A series of fMRI studies have evaluated

how hippocampal activity levels change over the course of AD: During the initial AD phase fMRI responses are higher than in normal controls, suggestive of compensatory mechanisms [55]. As the disease progresses, this pattern is reversed so that at the late MCI and early clinically probable AD stage fMRI activity levels in the same region are lower than in normal controls [55]. This sequence was also confirmed by a PS1 E280A mutation study [56, 36]: Hippocampal and parahippocampal responses are higher in presymptomatic mutation carriers aged between 18 and 30 years than in controls and precuneus is less deactivated [56, 36]. A similar sequence may occur in APOE $\epsilon 4$ carriers in the pre- or post-amyloid phase [57].

Adaptive mechanisms in AD have also been demonstrated using fMRI in the language domain [58, 59]. In MCI and early-stage AD, activity during associative-semantic processing in the left posterior superior temporal sulcus, a key region for lexical-semantic retrieval, is lower than in healthy controls [58, 59]. Response amplitude correlates with scores on confrontation naming and with speed of identification of written words. In the homotopical right-sided region, activity is higher in those AD subjects in whom confrontation naming is preserved compared to controls, suggestive of compensatory mechanisms [59].

In a third cognitive domain, executive functions, mainly prefrontal increases have been described [60, 61].

4.2 Intrinsic connectivity as a determinant of regional AD vulnerability

In vivo amyloid imaging has revealed the areas of predilection for amyloid aggregation in the earliest disease phase. These areas are precuneus, orbitofrontal cortex and anterior cingulate [62, 63, 64, 65, 66]. Intrinsic connectivity network analysis (ICN) [67, 68, 69, 70] has shed light on one of the most fundamental questions in neurodegenerative disease, the determinants of this regional vulnerability. Originally, the emphasis was on the concordance between one of the ICNs, the default mode network, and amyloid deposition [68]. However, amyloid deposition extends beyond DMN, even in the earliest stages of AD [57, 71]. More recently, the focus has shifted to determining which nodes within networks are most affected and why. A node's vulnerability is best predicted by a greater total connectional flow through that node and by a shorter functional path to the disease-related epicenters [70, 71]. Regional specificity of amyloid deposition therefore does not only depend on which network but also on the hub status of nodes within those networks [57]. Apart from its hub status, a high aerobic glycolysis index may also predispose to selective vulnerability [72].

5 Temporal ordering of in vivo imaging measures prior to clinical manifestations

A positive amyloid PET scan in a subject who does not show any cognitive deficits is a frequent occurrence, in particular with increasing age, rising from 5% between 50 and 60 years of age up to 50% above the age of 82 [73, 66, 74]. This asymptomatic stage [54] is referred to as the 'at risk of AD' stage by the International Working Group-2 [75], which reserve the term 'presymptomatic' for asymptomatic carriers of fully penetrant mutations. Theoretically, a distinction should be drawn between risk factors for cognitive decline, on the one hand, and biomarkers that reveal pathological changes before the disease becomes clinically manifest, on the other hand. For instance, APOEϵ4 carrier status is a risk factor and increases the risk of AD, in particular in women [76]. APOEϵ4 is also robustly associated with a higher risk of a positive amyloid scan in healthy controls [77, 31, 73, 66]. Other genetic polymorphisms, e.g. related to CR1 or Brain Derived Neurotrophic Factor (BDNF) codon 66 may also affect the amyloid burden according to preliminary evidence from case-control studies in smaller groups of subjects [78, 65].

The National Institute for Aging-Alzheimer Association (NIA-AA) nomenclature has introduced the term of preclinical AD [79], which implies that if a subject with preclinical AD lives long enough, he will develop clinical AD. The sequential order of biomarker positivity as specified by Jack et al. [18] has laid the foundation for the NIA-AA criteria for preclinical AD [79]: Stage 0 corresponds to cases with normal cognition, normal amyloid load and normal hippocampal volume, stage 1 to cases with amyloid positivity, stage 2 to cases with amyloid positivity *and* hippocampal volume loss, and stage 3 to cases with subtle cognitive changes, amyloid positivity *and* hippocampal volume loss.

Soon after this NIA-AA preclinical AD research staging was proposed, it was clear that the combinations of amyloid and structural MRI findings seen in reality on a relatively frequent basis did not conform to the predictions based on the sequential model [18]. According to a support vector machine analysis of the phase 2 ^{18}F-flutemetamol study, structural MRI scans show more often an AD-like pattern in cognitively intact controls than amyloid scans do [80]. In an MCSA series of 286 cognitively intact healthy controls, more than half showed imaging abnormalities, with the largest group (n = 69) showing hippocampal volume loss while being amyloid negative [81], a phenomenon dubbed 'suspected non-Alzheimer Pathophysiology' (sNAP). The sNAP group does not differ in any other respect from the preclinical AD cases in stage 2 or 3, e.g. in terms of regional brain volume loss or FDG PET regional hypometabolism [82]. In other words, they are classified as non-AD because of the absence of amyloid-positivity but are otherwise not distinguishable from

the preclinical AD cases.

In amyloid-positive cognitively intact subjects, studies of cortical thinning yields a rather different picture from hippocampal volumetry. At a time when hippocampal volume is still within the normal range, amyloid positivity in healthy controls is associated with cortical thinning in posterior cingulate/precuneus, inferior parietal, rostral middle frontal, and superior temporal cortex [24, 83]. Early structural changes in neocortex which precede changes of the hippocampal formation were also reported in the PS1 E280A kindred: Parietal volume was lower in the carriers even before amyloid load increased, similarly to what had been previously described in APOE $\epsilon 4$ carriers [36]. Amyloid-positivity in cognitively intact controls is also associated with a disruption of intrinsic connectivity between the precuneus and a large number of other regions [84].

6 Amyloid load and the path towards cognitive decline

sNAP subjects are as likely to progress within one year as subjects in NIA-AA preclinical AD stage 1 (10%) and more likely than subjects in phase 0 (5%). If subjects are both amyloid-positive and have hippocampal atrophy (stage 2), they are more likely to progress than subjects who have either of the two abnormalities (21%) [85]. Genetic risk factors beyond APOE may also affect the risk of cognitive decline in amyloid-positive cognitively intact subjects. Among amyloid-positive subjects, BDNF codon 66 *met* carriers experience faster cognitive decline (episodic memory, executive function, language) over 36 months period [86].

The prevalence of a positive amyloid scan in MCI is approximately 50-70% [8, 87, 10]. Amyloid-positive subjects with MCI are much more likely to progress to dementia within 20-24 months than amyloid-negative subjects (50-67% versus 5-19%) [88, 89, 9, 90, 87]. Among amyloid positive subjects with MCI, hippocampal atrophy predicts shorter time-to-progression while Aβ load does not [88]. In contrast, when amyloid-positive and amyloid-negative subjects with MCI are combined, hippocampal atrophy and Aβ load predict shorter time-to-progression with comparable power (hazard ratio for an inter-quartile difference of 2.6 for both) [88].

Among patients with MCI, a significant portion (15-30%) have pathological hippocampal volumes with normal amyloid levels [91, 10], called MCI-sNAP [10]. These patients are also at risk for progression, and, according to at least one study involving MCSA and ADNI cases, more so than amyloid-positive MCI cases who have normal hippocampal volumes [10]. Similarly to the progression rates seen in sNAP, the rate of cognitive decline in MCI-sNAP suggest that there are other pathways to cognitive decline than the amyloid-triggered pathway and that these pathways occur

with a relatively high prevalence.

7 Conclusion

Amyloid positivity is by definition and convention considered a necessary condition for classifying a case as AD. Cases who do not follow the course specified by the sequential model are assigned to a non-AD category [92]. The time course of the MRI volume changes are represented in the sequential model only in so far that the MRI volume changes are due to amyloid aggregation [92]. Other changes affect the brain e.g. due to aging, vascular factors, other proteinopathies... Hence the occurrence of MRI changes in the absence of amyloid-positivity, which may sometimes resemble the MRI pattern seen in AD (sNAP and MCI-sNAP). The proportion of patients with an amnestic MCI or a clinically probable AD phenotype who are amyloid-negative was clearly under-estimated prior to the advent of amyloid imaging. This highlights the importance of non-amyloid triggered pathways to cognitive decline in the general population as well as in clinical practice.

The multidimensional model is complementary to the sequential model and attempts to accomodate the diversity of processes and trajectories that can be seen in older adults, without a priori restriction to a conventional category of 'pure AD'. Importantly, the multidimensional model is not meant as an alternative or a criticism of the sequential model but incorporates the trajectories as specified by [18]. Evidently, despite the huge progress enabled by amyloid imaging, our ability to measure relevant pathophysiological processes in vivo in humans is still in its infancy. As more tools become available to carve out the causal-mechanistic space of cognitive decline in vivo in individual cases, we expect a still wider variety of combinations that cross the boundaries between conventional disease categories.

Regardless of which model one prefers, the primary goal is to identify druggable targets in individuals. The multidimensional model builds on the molecular hub-and-network approach to AD [16]. Starting from a descriptive level, it will hopefully pave the way for intervention in a personalized manner which is broader than using amyloid-lowering treatment on its own.

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